REMARKS

I. Claim Status

Upon entry of this Reply to Office Action, claims 24-30 and 33-42 will remain pending in this application, and claims 31-32 are canceled. Of those pending claims, claims 36-39 and 41 are currently withdrawn. By this Reply to Office Action, Applicant proposes to amend independent claims 24, 26, and 28. The specification fully supports the amendments to claims 24, 26, and 28 Support for the term "isolated or purified" may be found in the specification on page 20, lines 4 and 11. Support for the sera from individuals who are infected with the hepatitis B variant HDB 05 comprise an antibody which recognizes said oligopeptide or polypeptide may be found in the specification on page 20-21. Support for the number of consecutive amino acids (6) may be found in the specification on page 12-13. No new matter has been added.

Applicant addresses the objections and rejections below.

II. Election/Restriction Requirements

The Office withdraws claims 36-39 and 41 from further consideration pursuant to 37 C.F.R. § 1.142(b), as allegedly being drawn to a nonelected invention. The requirement is made FINAL.

Applicant respectfully traverses this rejection and reserves the right to file a petition at the appropriate time.

III. Rejections Under 35 U.S.C. § 101: Non-Statutory Subject Matter

The Office rejects claims 24-33, and 40 under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter. According to the Office, these claims are drawn to "[a]n oligopeptide or polypeptide comprising an amino acid sequence with at least 94% identity to SEQ ID NO:13." and the application

teaches that SEQ ID NO:13 is a fragment of the HBsAg protein from an HBV isolated from a patient. The Office asserts that the claims do not require that the oligopeptide or polypeptide is isolated or purified. Thus, the claims read on a protein comprising SEQ ID NO:13, wherein the protein may be part of the indicated HBV virus. The Office further asserts that the claims therefore read on a protein that may be found in nature, and on the virus that is found in nature.

Applicant respectfully traverses this rejection. As amended, all of the claims are directed to an oligopeptide or polypeptide which has been isolated or purified. Thus, in contrast to the Office's contention that the claims encompass non-statutory subject matter, the oligopeptide or polypeptide claimed reflects the hand of man. Specifically, Applicant amends independent claims 24, 26, and 28, to recite "isolated or purified" oligopeptide or polypeptide. Support for the amended claims can be found throughout the specification, for example, in the specification on page 20, lines 4 and 11. Applicant submits that the amended claims comply with the statutory subject matter requirements. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. § 101. Moreover, claims 31-32 have been canceled, making their rejection moot.

IV. Rejections Under 35 U.S.C. § 112 ¶ 2: Indefiniteness

The Office rejects claims 28, 30-35, 40, and 42 under 35 U.S.C. § 112 ¶ 2 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office treats claim 28 as representative. According to the Office, claim 28 reads on a peptide comprising "at least 5 consecutive amino acids from SEQ ID NO:12, and comprising at least one" of

the indicated amino acid positions of that sequence. The Office asserts that it is not clear from the claim language if the claim is requiring that the consecutive amino acid sequence from SEQ ID NO:12 includes the indicated amino acid position, or if the claim is requiring a consecutive sequence from SEQ ID NO:12, and an amino acid position corresponding to that identified amino acid positions. The Office further asserts that through the inclusion of claim 31, which specifies the amino acid found at the identified amino acid positions, it is implied that any amino acid may be present in the amino acid positions corresponding to the identified amino acid positions in the polypeptide of claim 28. In addition, the Office asserts that is it not clear what is meant by the language requiring that the polypeptide comprises one of the indicated amino acid positions and whether the claim is requiring that the polypeptide includes the identified position, includes the identified position having the same amino acid that is found in the identified position of SEQ ID NO:12, or if the polypeptide need only include the amino acid found in the identified position of SEQ ID NO:12. The Office requests clarification of the scope of the claims.

Applicant respectfully traverses this rejection. Again, using claim 28 as representative, the claim is directed to an oligopeptide or polypeptide comprising at least 6 (as amended) consecutive amino acids from SEQ ID NO:12, wherein said amino acids comprise at least one of the amino acids found at positions 73, 78, 112, 122, and 139 of SEQ ID NO:12. The claimed oligopeptide or polypeptide is specified as comprising at least 6 amino acids from SEQ ID NO:12 and the amino acids are specified as comprising at least one of the amino acids found at positions 73, 78, 112, 122, and 139 of SEQ ID NO:12. Having the amino acid position 73 in the claim implies

that the sequence may comprise the same amino acid as in amino acid position 73 of SEQ ID NO:12. Thus, in contrast to the Office's contention that the claims are indefinite, the oligopeptide or polypeptide claimed is definite. Solely to expedite prosecution, however, and without acquiescing to the rejection, Applicant amends independent claim 28, to further clarify the scope of the claims. Support for the amended claim can be found throughout the specification, for example, in the specification on page 12-13. Applicant submits that the amended claim complies with the statutory subject matter requirements. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. § 112 ¶ 2. Moreover, claims 31-32 have been canceled, making their rejection moot.

V. Rejections Under 35 U.S.C. § 112 ¶ 1: Written Description

The Office rejects claims 25, 40, and 42 under 35 U.S.C. § 112 ¶ 1 as allegedly failing to comply with the written description requirement. According to the Office, claim 25 is drawn to a genus of polypeptides comprising any polypeptide that is at least 94% identical to SEQ ID NO:13 (a fragment of the Hepatitis B surface antigen-HBsAg from HBV variant HDB 05), and that retains the ability to bind to sera from an individual infected with HBV variant HDB 05. Claims 40 and 42 read on kits or methods for the use of polypeptides that are at least 94% identical to SEQ ID NO:13 for the purpose of detecting antibodies against HBV. The Office takes the position that these claims therefore implicitly require that the polypeptides are capable of binding sera from HBV infected patients (or at least antibodies that bind to HBV) and are drawn to a genus of polypeptides having a sequence of at least 94% identity to SEQ ID NO:13, wherein the polypeptides react with either HBV or HBV variant HDB 05 reactive sera. The Office

asserts that the application indicates that SEQ ID NO:13 itself does not react to anti-HBV antibodies generally, and fails to identify any variants of SEQ ID NO:13 that bind to either anti-HBV or anti-HBV HDB 05 antibodies. The Office also asserts that there is significant uncertainty as to the ability of mutants of SEQ ID NO:13 to react with antibodies directed to either HBsAg proteins comprising SEQ ID NO:13 or to HBsAg proteins from other HBV variants. The Office therefore rejects the claims as lacking adequate descriptive support for the claimed genus of polypeptide comprising mutants of SEQ ID NO:13.

Applicant respectfully traverses this rejection. In making the written description rejection, the Office has overlooked that written description support does not require absolute, word-for-word support in a patent application text. In fact, literal support is not even the standard, as claims may also be supported implicitly or impliedly from the application as a whole. "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." M.P.E.P. § 2163. Possession can be demonstrated by "describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *Id.* (quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

As amended, claim 25 is directed to an isolated or purified oligopeptide or polypeptide comprising an amino acid sequence with at least 94% identity to SEQ ID NO:13, which reacts with sera from individuals who are infected with the hepatitis B variant HDB 05. The claim satisfies the written description requirement because a

skilled artisan could identify all of the nucleic acids encoding a polypeptide sharing at least 94% sequence identity with SEQ ID NO:13. These sequences were contemplated by the inventors as within the scope of their invention, and the specification teaches the relationship between the structure of these sequences and their function.

For example, the specification describes the claimed invention as a novel sequence having 5 amino acid substitutions in the HBsAg, with 4 substitutions being located in the region of the "a" determinant (aa 101 to aa 180) and 1 substitution in the direct vicinity thereof (aa 181). (See specification, page 1 and Example 4 on page 45.) A total of at least 5 partially overlapping epitopes on the a determinant between amino acid position 101 and 180 are assumed to be binding sites for antibodies, as has been demonstrated by using monoclonal antibodies. (See specification, page 5 and Figure 1 and 2.) The amino acid sequence shown in SEQ ID NO:13 corresponds to amino acid positions 111 to 185 of HBsAg. (See specification, page 10. SEQ ID NO:13 comprises the "a" determinant which acts as the binding sites for antibodies.) SEQ ID NO:13 (amino acid length 75) having 4 substitutions in the "a" determinant would result in a mutant of SEQ ID NO:13 being at least 94% identical to SEQ ID NO:13. The specification provides guidance regarding the structural features responsible for the functional activity. In addition, the specification recites an amino acid sequence which has at least 94% identity with SEQ ID NO:13 and falls within the scope of the invention, as well as amino acid sequences having at least 95%, 96%, 97%, 98% and 99% identity with SEQ ID NO:13. (See specification, page 10.)

The specification adequately describes the recited genus and a person skilled in the art can "visualize or recognize the identity of the members of the genus" under the

standard of *University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997). Thus, in contrast to the Office's contention that the claims fail to comply with the written description requirement, the claims are fully supported by the application. Support for the claims can be found throughout the specification. Applicant submits that the amended claims comply with the written description requirements. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. § 112 ¶ 1.

VI. Rejections Under 35 U.S.C. § 112 ¶ 1: Enablement

The Office rejects claims 24, 26, 33-35, 40, and 42 under 35 U.S.C. § 112 ¶ 1 as allegedly lacking enablement for the use of any polypeptide comprising an amino acid sequence of at least 94% identity to SEQ ID NO:13. The Office asserts that the claims broadly read on a genus of proteins comprising any protein of at least 94% identity to SEQ ID NO:13. According to the Office, the only example of such protein provided in the application is that of SEQ ID NO:13 itself. Thus, according to the Office, the application provides only limited teaching with respect to mutants of SEQ ID NO: 13, and the uses which mutants of the protein may be applied. The Office asserts that there is significant uncertainty in the ability of mutants of SEQ ID NO:13, even those with as few as one amino acid change, to interact with other anti-HBV HBsAg antibodies, or even with antibodies specifically directed to the HBsAg from which SEQ ID NO:13 was derived. According to the Office, there is insufficient information provided to enable those in the art to use the claimed polypeptides without undue experimentation.

Applicant respectfully traverses this rejection. In making the enablement rejection, the Office is improperly using working example to limit scope of claim. Claims

24, 26, 33-35, 40, and 42 are directed to an isolated or purified oligopeptide or polypeptide comprising an amino acid sequence with at least 94% identity to SEQ ID NO:13. A skilled artisan could identify all of the nucleic acids encoding a polypeptide sharing at least 94% sequence identity with SEQ ID NO:13. The specification is enabling where it teaches "those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997). However, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

When combined with the knowledge in the art, the specification provides substantial guidance to enable the skilled artisan to make and use the claimed proteins claimed. Working examples for isolating and validating the claimed proteins are also provided in the specification, and these methods could be applied easily to the claimed variants. (See specification, page 38-39, Example 1 on page 42 and Example 2 on page 43.) Therefore, one of skill in the art could practice the invention by following the steps provided by the working examples, which further support enablement of the claimed proteins. For example, it would be very easy to determine whether the claimed variants have the same activity as SEQ ID NO: 13 (for example, as measured by binding to antibodies in sera from individuals who are infected with the hepatitis B variant HDB 05). These antibodies could easily be used in the sandwich immunoassay of Example 1 and it would be very easy for the skilled artisan to determine whether a variant was active as contemplated by the invention. Multiple variants could be tested

at the same time as the assay is conducted on a microwell plate. Therefore, undue experimentation is not required for one of skill in the art to prepare proteins that meet the functional limitations of the claims and to practice the invention. Such experiments would involve merely repeating the experiments disclosed in the specification and repetition of such experiments would constitute routine screening.

The invention is in the area of biotechnology. While biotechnology may be an unpredictable art, that does not preclude a finding of enablement. See, e.g., *Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In *Wands*, the court concluded that the production of monoclonal antibodies was routine, and that claims to monoclonal antibodies of a particular affinity were enabled. Similarly, cloning and testing proteins for activity is routine. Applicant respectfully asserts that the claims are not overly broad in view of the nature of the invention.

The state of the prior art was that production of proteins and testing for activity (such as binding to known antibodies) was routine. (See specification, page 38-39.) In addition, detection of proteins by Western blotting or other immunoassay is a standard technique. It is very common and easy to make protein variants and to test them for binding to antibodies. One of skill in the art could easily make proteins and test for their activity, which would only require following the guidance provided by the specification, including the working examples. Applicant respectfully submits that the state of the art, when combined with disclosure in the specification, supports enablement of the claims.

A skilled artisan could identify all of the nucleic acids encoding a polypeptide sharing at least 94% sequence identity with SEQ ID NO:13. A skilled artisan could also

determine whether these sequences share the activity of SEQ ID NO: 13, such as for example defined by binding to known antibodies.

A skilled artisan could apply the teachings of the specification to additional species and practice the claimed kit by following the direction provided by the specification without undue experimentation. Thus, in contrast to the Office's contention that the claims fail to comply with the enablement requirement, the claims are fully supported by the application. Support for the claims can be found throughout the specification. Applicant submits that the amended claims comply with the enablement requirement. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. § 112 ¶ 1.

VII. Rejections Under 35 U.S.C. § 102(b): Anticipation over Quinnan *et al.* (WO 00/07631)

The Office rejects claims 28 and 31 under 35 U.S.C. § 102(b) as allegedly being anticipated by Quinnan *et al.* (WO 00/07631). The Office takes the position that the claim is read as including any polypeptide comprising 5 consecutive amino acids of SEQ ID NO:12, wherein the consecutive sequence includes an amino acid corresponding to position 73 of that sequence. The Office also takes the position that the Applicant identifies the sequence of TRTST as such a sequence. The Office asserts that Quinnan anticipates the indicated claims because it teaches a polypeptide comprising such a sequence. (Response of August 2008, top of page 9.) Quinnan *et al.* (WO 00/07631), page 27 (SEQ ID NO:4 of the reference includes the sequence TRTST).

Applicant respectfully traverses this rejection. SEQ ID NO:4 of Quinnan appears to be unrelated to the claimed SEQ ID NO:12 and does not appear to be an HBsAg

sequence. Instead, it is related to an HIV-1 Envelope Protein. Solely to expedite prosecution, however, and without acquiescing to the rejection, Applicant amends independent claim 28 to recite sequences comprising at least 6 amino acids, wherein said amino acids comprise at least one of the amino acid found at positions 73, 78, 112, 122, and 139 of SEQ ID NO:12. Support for the amended claims can be found throughout the specification, for example, in the specification on page 12-13. Applicant also provides a chart below that compare SEQ ID NO:12 to the equivalent portion of Quinnan's sequence. Differences are shown in bold text.

Pos. No.	71	72	73	74	75	76	77
SEQ ID NO:12	**S**	T	R	T	S	T	**G**
Quinnan's Sequence	**N**	T	R	T	S	T	**T**

Any sequence of at least 6 consecutive amino acids from SEQ ID NO:12 that includes TRTST spanning amino acid positions 72 to 76 must include at least one of positions 71 or 77 as well. Quinnan does not teach or suggest an amino acid sequence comprising STRTST or TRTSTG. Applicant submits that the amended claims overcome the anticipation rejection. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b). Moreover, claim 31 has been canceled, making its rejection moot.

VIII. Rejections Under 35 U.S.C. § 102(b): Anticipation over Langley *et al.* (EP 0533492)

The Office rejects claims 28, 33-35, and 40 under 35 U.S.C. § 102(b) as allegedly being anticipated by Langley *et al.* (EP 0533492). The Office takes the position that the claim 28 is read as requiring that the claimed polypeptide includes a position corresponding to the identified position of SEQ ID NO:12, but not necessarily

requiring that the same amino acid be found in that position. The Office also takes the position that claim 34 and 35 require the recombinant production of the peptide, and the purification of such from other polypeptides. The Office asserts that Langley anticipates the indicated claims because it teaches an HBsAg protein sharing at least 5 consecutive amino acids with SEQ ID NO:12, and comprising an amino acid corresponding to position 73 of SEQ ID NO:12. Langley, Figure 1 (showing sequence encoding by SEQ ID NO:1 of the reference), and claims 1-10. The Office also asserts that Langley anticipates the indicated claims because it teaches the recombinant production and purification of the protein. (Langley, pages 6-7.)

Applicant respectfully traverses this rejection. This rejection is now moot due to the amendments to claims 28 and cancelation of claims 31-32. The Office is incorrect in its interpretation of claim 28 that it is read as "requiring that the claimed polypeptide includes a position corresponding to the identified position of SEQ ID NO:12, but not necessarily requiring that the same amino acid be found in that position." As amended, claims 28 now recites "An isolated or purified oligopeptide or polypeptide comprising at least 6 consecutive amino acids from SEQ ID NO:12, wherein said amino acids comprise at least one of the amino acid found at positions 73, 78, 112, 122, and 139 of SEQ ID NO:12." Applicant submits that the amended claims overcome the anticipation rejection. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. §102(b).

IX. Rejections Under 35 U.S.C. § 103(a): Non-obviousness over Quinnan *et al.* (WO 00/07631 - supra)

The Office rejects claims 34 and 35 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Quinnan *et al.* (WO 00/07631 - supra). The Office takes the position

that these claims read on methods of recombinantly producing the peptides of claims 28 and 31. According to the Office, Quinnan teaches peptides meeting the limitation of these claims and that the reference also teaches that proteins and peptides of the invention may be prepared by any available means, including recombinant expression. (Quinnan, page 8.) The Office asserts that Quinnan renders the claimed methods obvious because, while the reference does not specifically teach such expression and isolation of the polypeptide of SEQ ID NO:4 of that reference, it would have been obvious from these teaching to one of ordinary skill in the art that such recombinant expression methods could also be used for this polypeptide.

Applicant respectfully traverses this rejection. This rejection is now moot due to the amendments to claims 28 and 31. As amended, claim 28 now recites "An isolated or purified oligopeptide or polypeptide comprising at least 6 consecutive amino acids from SEQ ID NO:12, wherein said amino acids comprise at least one of the amino acid found at positions 73, 78, 112, 122, and 139 of SEQ ID NO:12." Quinnan does not teach peptides meeting the same limitation. Claim 31 has been canceled, making its rejection moot. Applicant submits that the amended claims overcome the non-obviousness rejection. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

X. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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